Drugs Believed Capable of Inducing Autoimmune Hepatitis

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Immune-Mediated Liver Diseases

There are two broad categories of immune-mediated liver disease:

- Autoimmune hepatitis (AIH) presenting as hepatocellular disease
- Primary biliary cirrhosis (PBC) and Primary sclerosing cholangitis (PSC) presenting as cholestatic liver disease

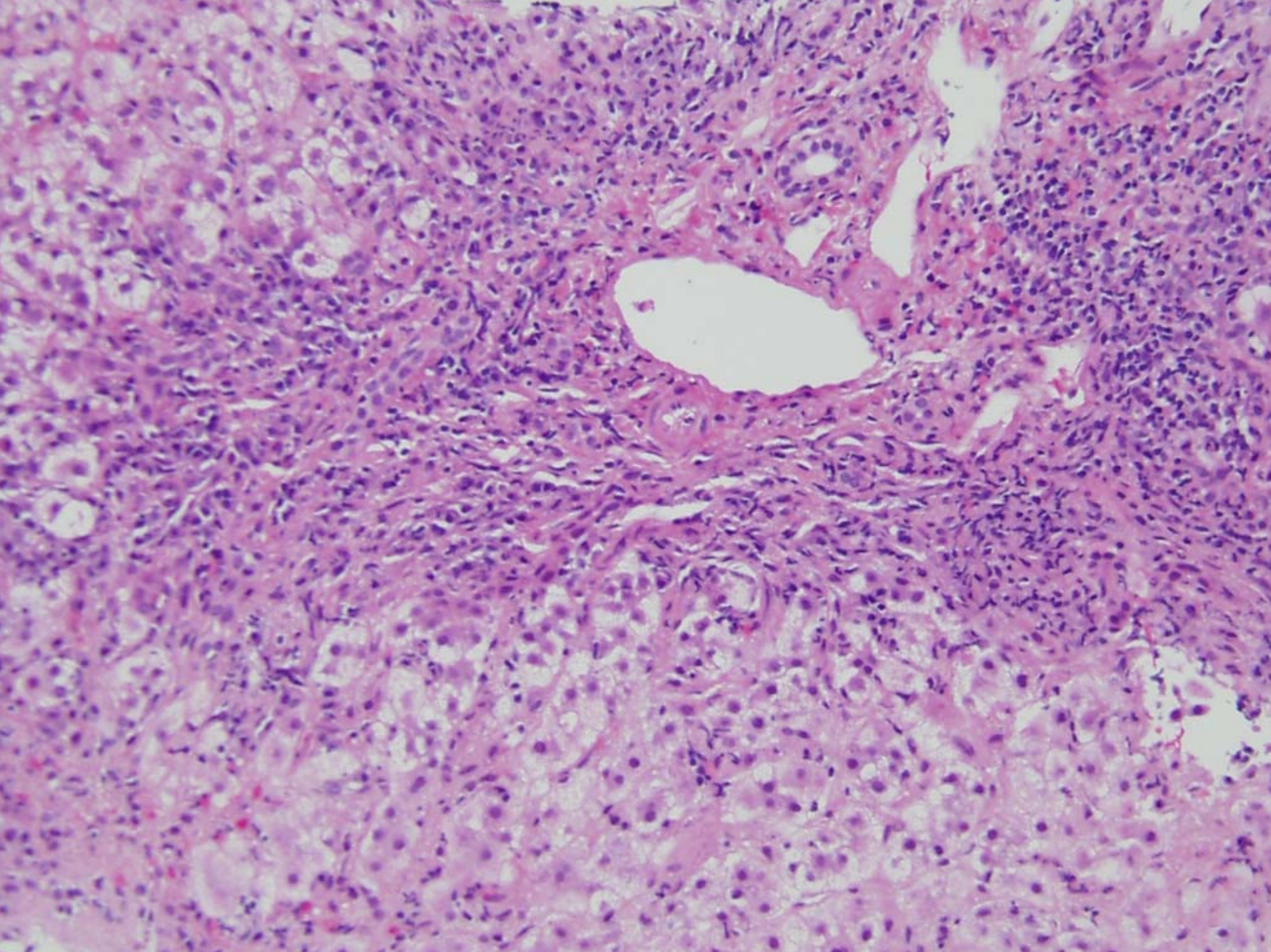
Drug-Induced Immune Mediated Liver Disease

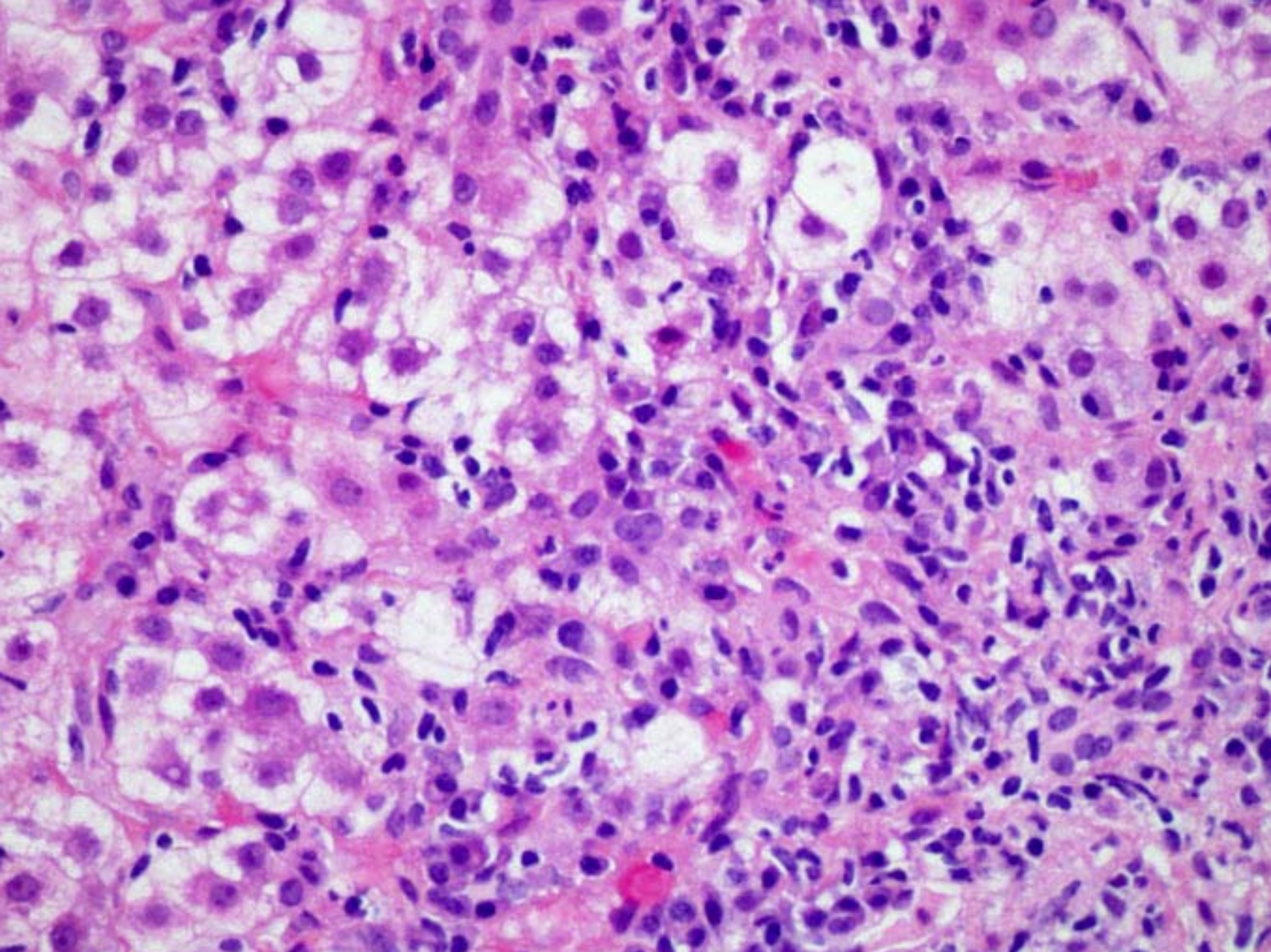
Drugs are believed capable of inducing both the hepatocellular and cholestatic forms of immunologically-mediated liver disease

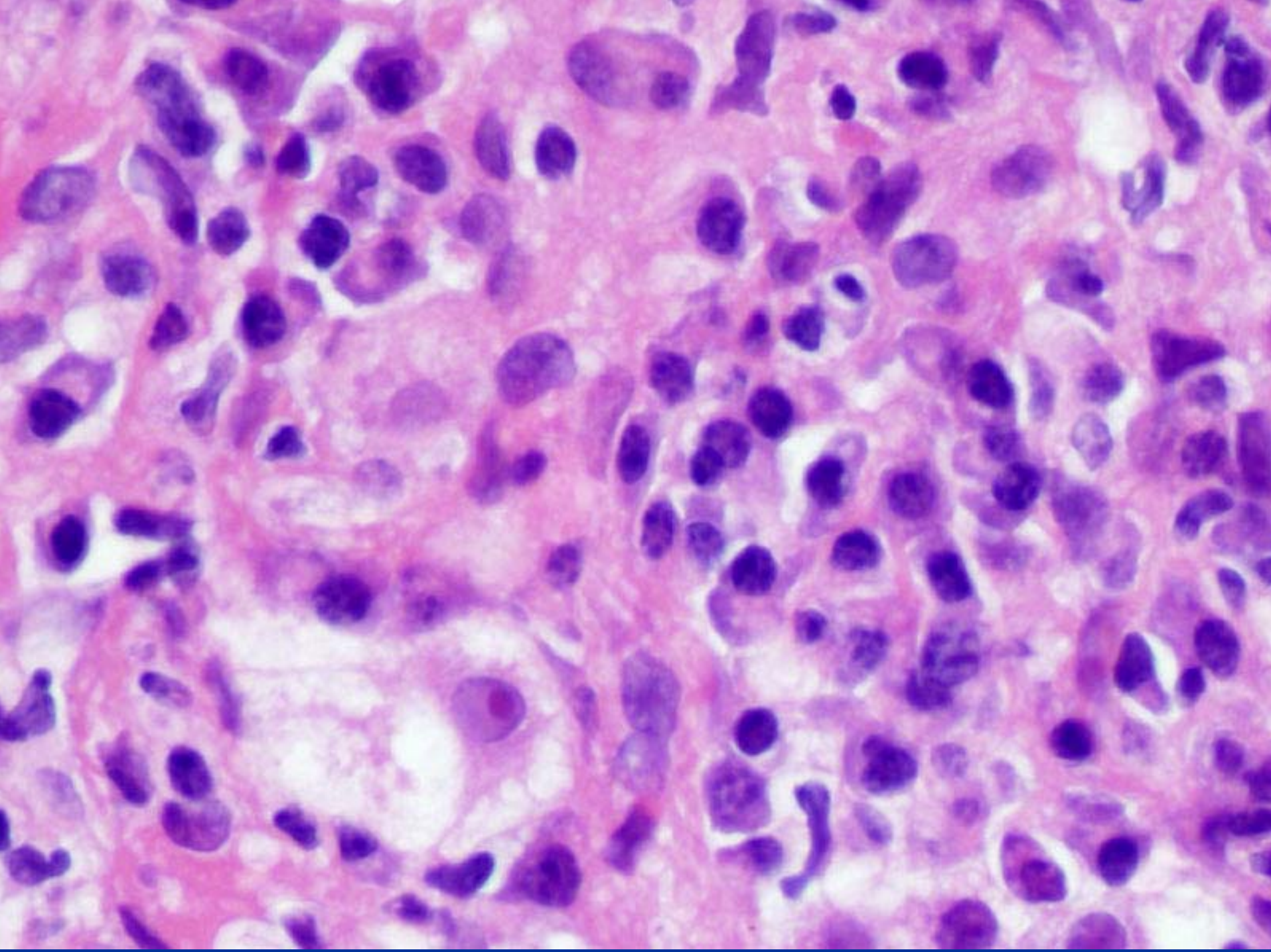
This presentation focuses only on the condition of autoimmune hepatitis

Manifestations of Autoimmune Hepatitis

Gender: Predominantly female
Clinical: Fatigue, RUQ discomfort, jaundice, mild pruritis, arthralgias
Biochemical: Raised bilirubin, ALT, AST, ±AP gammaglobulin
Autoantibodies: ANA, LKM1, SLA/LP
HLA: B8, DR3,DR4,C4AQO
Histology: Interface hepatitis, plasma cells, ±fibrosis, ±cirrhosis
Treatment: Responsive to immunosuppressives







Subclasses of Autoimmune Hepatitis

Feature	Type 1	Type 2	Type 3
Autoantibodies	ANA/SMA	LKM1	SLA/LP
Prevalence	80%	20%-Eur. 4%-U.S.	<20%
Age	16-30 >50	2-14	20-40
Extrahep. Dis	41%	34%	58%
HLA	B8, DR3, DR4	B14, DR3, C4AQO	Unknown
Cirrhosis	45%	82%	75%

Bantal and Manns

International Diagnostic Criteria for Autoimmune Hepatitis, 1999

Scoring system, with points awarded for:

Gender, serum biochemistry, serum globulins, autoantibodies, antimitochondrial antibody, hepatitis viral markers, genetic factors, drug history, alcohol intake, liver histology, response to treatment

Aggregate Score:

Pretreatment: Definite >15; Probable 10-15

Posttreatment: Definite >17; Probable 12-17

Etiology of Autoimmune Hepatitis

- Unknown in most instances
- Believed to occur in persons with inherited susceptibility
- Presumably requires a trigger to initiate the liver disease
- Potential triggers: Viral hepatitis A and C
  Other viruses (hepatitis B, EBV, HSV)
  Drugs

Drug-Induced Autoimmune Hepatitis
First Implicated Drug

Dialose Plus® (dioctyl sodium sulfosuccinate, carboxy methyl cellulose, oxyphenisatin acetate)

First report of hepatotoxicity – Munthe Fog,
Acta Medica Scand Supplement, 1949

Second report of hepatotoxicity – Reynolds et al,
JAMA 1970

Prolonged receipt by 4 women
Acute hepatocellular injury with jaundice
Abated after withdrawal but recurred
after deliberate or inadvertent re-challenge

Drug-Induced Autoimmune Hepatitis First Implicated Drug (contd.)

Dialose Plus® (dioctyl sodium sulfosuccinate, carboxy methyl cellulose, oxyphenisatin acetate)

First report of AIH – Reynolds et al, NEJM 1971

- Seven additional cases (6 women)
- Laxative given for at least one year
- Mod. to marked increase in serum enzymes, serum bilirubin, globulin levels
- Positive ANA, SMA, LE cell test
- Histology: "CAH" ±cirrhosis
- Improved after withdrawal of laxative

Over 100 cases since then; removed from market

Considerations in Linking Drugs to Autoimmune Hepatitis

Assuming development of liver injury resembling AIH temporally associated with receipt of a drug, what are the possible relationships?

1. Might there have been pre-existing but subclinical AIH that is identified for the first time through biochemical screening while performing evaluation for potential hepatotoxicity or that exacerbates known AIH?

Considerations in Linking Drugs to Autoimmune Hepatitis (contd.)

2. Might the drug have induced de novo liver injury that manifests as autoimmune hepatitis?

3. Might the drug have behaved as the trigger for development of AIH in a person with an inherited susceptibility?

Drugs Reported to Cause Liver Disease That Resembles Autoimmune Hepatitis, Type 1

Multiple Reports

- Oxyphenisatin
- Nitrofurantoin
- Minocycline
- Alpha-metyldopa
- Clometacine

Drugs Reported to Cause Liver Disease That Resembles Autoimmune Hepatitis, Type 1

Few Reports – Conventional Drugs

- Atomexitine
- Diclofenac
- Doxycycline
- Fenofibrate
- HMG-CoA reductase inhibitors (artorvastatin, rosuvastatin, simvastatin)
- Infliximab
- Interferon
- Papaverine
- Pemoline
- Phenprocoumon
- Rifampin + Pyrazinamide
- Twinrix

Drugs Reported to Cause Liver Disease That Resembles Autoimmune Hepatitis, Type 1

Few Reports – Herbal Compounds

- Dai-saiko-to
- Germander
- 3,4-methylenedioxymetamphetamine ("Ecstasy")
- Morinda citrifolia (Noni juice)

Drugs Reported to Cause Liver Disease That Resembles Autoimmune Hepatitis, Type 2

- Dihydralazine
- Tienilic Acid
- Halothane

How Does One Differentiate "Cryptogenic" From Drug-Induced Autoimmune Hepatitis

More likely to be "cryptogenic" if:

- AIH known to pre-date drug administration
- ANA known to pre-date drug administration
- Specific HLA genes identified
- Liver disease disappears on drug withdrawal (but see later)
- Affected person has other autoimmune disorders (e.g. thyroiditis, arthritis, etc)
- Presumed drug-related case only a single case report

How Does One Differentiate "Cryptogenic" From Drug-Induced Autoimmune Hepatitis

More likely to be "drug-induced" if:

- Multiple cases reported of a specific drug
- Specific HLA genes not identified
- Liver disease improves after drug withdrawal (but AIH triggered by drug might be self-sustaining)
- ANA disappears after drug withdrawal
- Recurrence of recovered liver disease with re-challenge

Drug-Induced Autoimmune Hepatitis
Final Words

It is very likely that drugs can trigger AIH
However, it can be difficult in the individual case to clearly establish the link
Future reports should require that:

- pre-existing AIH is unknown or excluded
- HLA characteristics be reported in addition to the autoantibodies
- impact in long-term follow-up of drug withdrawal on liver disease and ANA be reported